REMARKS

Applicant thanks the Examiner for the withdrawal of the prior pending rejections in view of Applicant's previous response to the Office. New grounds of rejection are addressed below.

Claim Amendments

Claims 2-3, 12, 17, 19-20, 22, 30, 32-33, 37-38, and 40-41 have been amended as presented above for clarity. New claims 68-77 have been added. Claims 1, 18, 21, 23, 39, and 65-67 have been cancelled. Claims 55-64 were previously cancelled. No new matter has been introduced by the addition of the new claims and they are fully supported by the disclosure.

Support for new claim 68 can be found, for example, in original claims 1 and 18 and paragraphs 0023, 0040, and 0061-0066 of the specification.

Support for new claim 69 can be found, for example, in original claim 1 and paragraph 0023 of the specification.

Support for new claims 70, 72, 76, and 77 can be found, for example, in paragraphs 0040 and 0061 of the specification.

Support for new claim 71 can be found, for example, in original claims 17-18 and paragraphs 0056, 0062-0066, and 0068 of the specification.

Support for new claim 73 can be found, for example, in paragraph 0063 of the specification.

Support for new claim 74 can be found, for example, in original claims 21 and 39 and paragraph 0024 of the specification.

Support for new claim 75 can be found, for example, in original claim 21 and paragraph 0024 of the specification.

Accordingly, entry of the new claims and amendments is proper and respectfully requested.

Patentability of Claims over the Art

Claims 1-3, 8, 10, 14-19, 21-24, 28, 30, 34-40, 41-54, and 65-67 stand rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent 5,207,752 ("Sorenson") in view of Palmeri *et al.*, J.Chemotherapy 1990, vol. 2(3), pp. 327-330 ("Palmeri"), and U.S. Patent 6,436,091 ("Harper"). Applicant submits that the claims pending after entry of this

amendment are patentable over the combination of references cited and requests prompt notification of allowability of the claims.

Sorenson is cited by the Office to show a devices and methods for introducing a therapeutic agent for a first interval, then introducing the same agent at a second lower interval, in order to achieve and maintain optimal drug levels. Sorenson does not teach internal pumps. Harper is cited by the Office to show osmotic, implantable pumps that can be regulated. Palmeri is cited to show the need for modulation of interferon α2a to reduce side effects and administration of different levels of interferon to achieve an optimal dosage. The combination is ineffective, however, in rendering obvious the above claims.

Sorenson, the primary reference applied by the Office in the rejection, discloses an external, iontophoretic pump that is designed for transdermal delivery, i.e. delivery across intact skin, of therapeutic agents. *See* Sorenson at column 1, lines 17-20, and column 6, lines 5-23. Typically, an initial high current is provided and maintained for a predetermined time to drive the agent into the body, ensuring that the initial drug concentration in the bloodstream reaches a temporary peak value. Thereafter, the delivery of high current is shut off for a delay period to allow for the drug concentration to subside to a maintenance level, and then further current is applied to allow operation of the pump in maintenance mode. While in the maintenance mode, Sorenson's pump may be stepped up to increase the drug concentration, such as with a user-activatable timer. Programming of the current delivery characteristics of Sorenson's pump is also contemplated. *See* column 1, line 67, to column 2, line 32, and claims. Sorenson's device is especially useful in a situation where a painkiller is administered to the patient and the scheme allows rapid input of drug to the bloodstream "while minimizing overshoot above the maximum desirable level of the therapeutic dose window for the drug". *See* column 2, lines 7-9.

In view of the nature of the device and methods taught in the reference, Applicant submits that Sorenson is non-analogous art and, as such, should not be used as the basis for a rejection under 35 U.S.C. § 103(a). Determination of the scope and content of the prior art is one of the key factual inquires necessary for a determination of obviousness under 35 U.S.C. § 103(a). *Graham v. John Deere*, 148 USPQ 459, 467 (S. Ct, 1966). A reference must be from analogous prior art if it is used as the basis for a rejection under 35 U.S.C. § 103(a). MPEP § 2141.01(a). Otherwise "the combination of elements from non-analogous sources, in a manner that reconstructs the applicant's invention only with the benefit of hindsight is

insufficient to present a *prima facie* case of obviousness." *In re Oetiker*, 24 USPQ2d 1443, 1446 (Fed. Cir. 1992).

Two criteria determine whether the prior art is analogous. *In re Deminski*, 230 USPQ 313, 315 (Fed. Cir. 1986). First, is the reference in the field of the inventor's endeavor? *Id.* If the reference is not in the field of the inventor's endeavor then the reference must be reasonably pertinent to the particular problem with which the inventor was concerned. *Id.* A reference is reasonably pertinent even if it is in a field different from the inventor's endeavor when it would have logically have come to the inventor's attention in considering his problem. *In re Clay*, 23 USPQ2d 1058, 1060 (Fed. Cir. 1992). The purposes of both the invention and the prior art are important in determining whether the reference is reasonably pertinent to the problem the invention attempts to solve. *Id.*

Other than broadly being useful as a drug delivery system, the devices disclosed by Applicant and by Sorenson are so different as to be considered non-analogous. Quite clearly, Sorenson does not teach a method that utilizes "an internally presented implantable pump that is not externally programmed." More directly, Sorenson's pump is an external pump that may indeed be programmed externally, so Sorenson's disclosure and Applicant's invention are clearly distinguishable. The invention taught by Applicant does not operate for the same purpose or in the same manner as the invention of Sorenson. While Sorenson's device teaches higher and lower electrical current levels, Applicant's methods utilize a pump that does not provide any electrical current whatsoever. While Sorenson's device teaches possibly incorporating a user-activatable switch, Applicant's methods utilize a pump that does not need intervention by the user. While Sorenson's device teaches stepping up the current level in the maintenance mode, e.g. such as through the use of a user-activatable switch, Applicant's methods "minimize[] or eliminate[] the need to alter the rate or change the dose-rate of the drug once long-term dosing has commenced with a long-term delivery system". *See* paragraph 0020.

Most importantly, the method of delivery taught by Sorenson is intended to provide the patient with an initial high peak level of drug concentration, followed by lower maintenance levels. This is in contrast with Applicant's method, which does not teach administration of a short-term formulation (presumably equated with Sorenson's initial high current delivery by the Office in the rejection) specifically to achieve an initial high peak level of drug concentration, although such an initial high peak level may exist in some cases. Instead, the purpose of the short-term formulation according to Applicant's invention is fine-

tuning of the appropriate dosage for the individual. A suitable dose is one that provides an appropriate level of therapeutic benefit for the patient. Applicant's specification clearly teaches that administration of the short-term formulation facilitates dose-individualization and the setting of a long-term administration scheme. *See* paragraphs 0018-0019. The short-term formulation is not "spiked" to a peak level, then allowed to drop off, and then stepped up further, as taught by Sorenson.

As noted above, to be suitable for a §103(a) rejection, the reference should be in the field of the inventor's endeavor and if not in the field, then it must be reasonably pertinent to the particular problem with which the inventor was concerned. Although the device taught by Sorenson is a drug delivery pump, it is an iontophoretic pump external to the patient's body for transdermal delivery of an agent, e.g. a painkiller, and it is controllable externally. As such, it is a drug delivery pump that is so different as to arguably *not* fall within the inventor's field of endeavor. If the field of endeavor is defined very broadly, however, to include all drug delivery pumps, it is still clear that Sorenson's pump is not reasonably pertinent to the particular problem with which the inventor was concerned. One addressing the problem faced by Applicant would not have logically looked to iontophoretic pumps for transdermal delivery of drugs for resolution of the problem. The purposes for the invention of Applicant and that of Sorenson are so distinct that the Sorenson reference must be considered as non-analogous art.

Assuming arguendo that the Sorenson reference is properly available for the purpose of a §103 rejection, Applicant submits that the Office has failed to establish a *prima facie* case of obviousness, nonetheless. It is well-established that the Office bears the initial burden of establishing a *prima facie* case of obviousness. *In re Bell* 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); MPEP § 2142. To establish a *prima facie* case, three basic criteria must be met: (1) the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention; (2) the prior art must provide one of ordinary skill with a reasonable expectation of success; and (3) the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. Thus, the ordinarily skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the Patent Office would be successful. *In re Dow Chemical Co.* 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988). The motivation to modify and/or

combine and the reasonable expectation of success, must come from the prior art, not Applicants' disclosure. *In re Vaeck* 20 USPQ2d 1438 (Fed. Cir. 1991).

In the present situation, the Office has failed to establish its *prima facie* case. As discussed above, Sorenson discloses a very different device for a very different purpose. Sorenson teaches an iontophoretic pump for transdermal delivery. Applicant teaches methods for the treatment of an interferon-responsive disorder or for individualizing doses of interferon or for manufacturing a long-term delivery device. Accordingly, Sorenson does not provide motivation or suggestion that would lead one of ordinary skill to arrive at the methods claimed by Applicant. As discussed further below, the secondary references applied by the Office also fail to provide such a motivation or suggestion. Thus, Applicant submits that an ordinary practitioner would not have been spurred by Sorenson, with or without further teachings in the art, to arrive at Applicant's invention. Even if the combination of references cited by the Office were permissible, Sorenson and its secondary references fail to teach each and every limitation of Applicant's claims 68, 74, and 41.

Harper teaches an implantable osmotic pump, optionally with a catheter system, having a series of impermeable and semipermeable barriers. The semipermeable barriers can be breached, as with a lancet, to alter the flow rate from the pump once the device has been implanted in the patient. Harper does not provide the necessary motivation or suggestion to combine the references, nor does it teach a method that comprises administering, adjusting, and selecting steps, as claimed by Applicant. Thus, although the Harper reference discloses osmotic pumps, it does not overcome the deficiencies of the Sorenson patent.

Nor does the Palmeri reference, which teaches a dose optimization study for treatment of advanced colorectal carcinoma, provide the suggestion to combine the references that could not be found in the other two. Even if such combination were impermissibly made, Palmeri, Sorenson, and Harper together would not lead one of ordinary skill in the art to arrive at Applicant's invention. Palmeri's identification of a maximally tolerated dose of recombinant alpha interferon 2a with 5-fluorouracil, and downward adjustment of doses prompted by ill effects in patients, if combined by the ordinary practitioner with the iontophoretic pump for transdermal delivery taught by Sorenson and the externally regulatable osmotic pump of Harper would lead simply to teachings of two types of pumps and an advanced colorectal carcinoma dose optimization study. Such combination would not, however, lead one to methods of treatment or methods of individualizing doses having short-term and subsequent long-term interferon formulation administration steps, wherein the long-

term formulation is released from an internally presented implantable pump that is not externally programmed, as taught in the instant application. Nor would such combination of art lead to a method of manufacture wherein standard and reduced rate long-term delivery devices are prepared and such devices release drug from implantable pumps that are not externally programmed and are suitable for internal presentation, as taught in the instant application.

The Office has thus failed to establish a *prima facie* case in this instance. The Sorenson, Harper, and Palmeri references would not provide one of ordinary skill with any motivation or suggestion of combining their teachings to thereby arrive at Applicant's invention. Particularly in view of the very different purpose and manner of operating presented in the Sorenson patent, one of ordinary skill would not look to what could arguably be considered non-analogous art and combine it with other teachings to arrive at the methods taught by the Applicant. Even if the references were to be considered in combination, they would not teach or suggest each and every limitation of the invention. Applicant therefore submits that the currently pending claims are not obvious in light of the Sorenson, Harper, and Palmeri references.

Claims 4-7, 9, 12, 13, 20, 25-27, 29, 32, and 33 were rejected under 35 U.S.C. § 103(a) as unpatentable over the above references and further in view of Johnson *et al.*, Scientific American, May 1994, pp. 68-75 ("Johnson"). Johnson discusses the treatment of various disorders and medical conditions with the use of various types of interferons. For example, interferon-alpha may be used for treatment of chronic hepatitis B and C, hairy-cell leukemia, and Kaposi's sarcoma; interferon-beta may be used for treatment of relapsing-remitting multiple sclerosis; interferon-gamma may be used for treatment of chronic granulomatous disease. Johnson's teaching of such uses of interferons fails, however, to add the requisite motivation, suggestion, or indeed the appropriate level of detail to overcome the deficiencies to the earlier cited references. One making the combination, nonetheless, would not have the benefit of the hindsight provided by Applicant's disclosure and would not arrive at the methods of independent claims 68, 74, and 41, nor their dependent claims.

U.S. Patent No. 4,847,049 ("Kwan") was also applied by the Office, in combination with Sorenson, Harper, and Palmeri to reject claims 11 and 31 under 35 U.S.C. § 103(a). Kwan teaches an interferon formulation including thimerosal, a preservative. Claims 11 and 31 specify that in some embodiments the short-term and the long-term formulations are different. The rejection is respectfully traversed. The teachings of Kwan in combination

with the Sorenson, Harper, and Palmeri references fail to make obvious claims 11 and 31 because the disclosure of the particular formulation of Kwan adds little to the shortfalls of the other references. Applicant submits that one of ordinary skill could not look to Kwan's teaching of the given formulation of interferon and find a suggestion or motivation to combine it with Sorenson, Harper, and Palmeri to arrive independently at the invention taught by Applicant. Even if such a suggestion were to be found, Kwan fails to add the necessary elements to the other references to render Applicant's claims obvious.

The references cited do not provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings to arrive at Applicant's invention. In fact, the primary reference relied upon by the Office is arguably from a non-analogous field and the ordinary practitioner would not have looked to its teachings to address the problem presented in Applicant's situation. Even if the ordinary practitioner would somehow look to Sorenson and the other cited references and impermissibly use the hindsight provided by Applicant's disclosure to combine the references, he would find that the references as a whole do not teach or suggest each and every limitation of Applicant's claims.

Applicant submits, therefore, that the claims pending after entry of this amendment are patentable. Applicant requests prompt notification of allowability of the claims. If any issues remain, the Examiner is invited to call the undersigned representative of Applicant directly at (415) 781-1989.

Respectfully submitted,

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